REMARKS

I. Status of the Claims

Claims 1-5, 12-14, 16-66, 73, 74, 78-85, 87-92 and 100 are pending. Applicants note that pursuant to the Petition Decision, the finality of the Office Action dated May 13, 2010 was withdrawn, the restriction requirement between Groups I-XIII was withdrawn and claims 82-85, 87-92 and 100 were rejoined for examination.

II. Amendments

In view of the withdrawal of the finality of the Office Action dated May 13, 2010 and the consequent re-opening of prosecution, Applicants enter herewith an amendment to the claims. Applicants note that the amendment made on August 13, 2010 was entered, and the present claims are marked up relative to that amendment.

Claim 1 is amended by inserting an option for R_2 based on a definition found at p. 25 beginning line 4 of the application.

Claim 101 is added and drawn to an embodiment described, for example, in the paragraph beginning at p. 26 line 21 of the application.

Claim 102 is added and drawn to an embodiment described, for example, in the paragraph beginning at p. 27 line 1 of the application.

Claim 103 is added and drawn to an embodiment described, for example, in the paragraph beginning at p. 27 line 13 of the application.

Claims 104-109 have been added which recite embodiments disclosed in the specification in the paragraphs beginning on p. 35 line 20, p. 37 line 8, p. 38 line 2 and p. 26 beginning at line 10.

III. Response to the Outstanding Objections and Rejections

A. Response to the Objection to the Claims for Containing Allegedly Improper Markush Language

The Advisory Action dated October 14, 2010 continued to maintain that the language of claim 1 was "not proper Markush language."

As Applicants pointed out previously, this is incorrect. Applicants further note that the Office Action dated May 13, 2010 and the Advisory Action dated October 14, 2010 both failed to provide any *reasons* why the alternative language in claim 1 was considered to be improper.

The preamble of claim 1 uses the following language:

- A compound **selected from** compounds of Formula (**Ia**) **and** pharmaceutically acceptable salts, hydrates, and solvates thereof ...

This expression is clearly a form of alternative expression that is recognized as being proper in the MPEP. MPEP 2173.05(h) identifies at least two different forms are acceptable for reciting alternatives in a claim. MPEP 2173.05(h) explains that "[o]ne acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being 'selected from the group consisting of A, B and C.' See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925)" and that in addition "[a]lternative expressions using 'or' are acceptable, such as 'wherein R is A, B, C, or D.'" Thus, the following formats are both acceptable according to the MPEP:

- ...wherein X is **selected from** the group consisting of A, B, C **and** D;
- ...wherein X **is** A, B, C **or** D.

It should be apparent from the wording of claim 1 that Applicants' claims use a variant of the first form "Markush" claim language, i.e. where X is **selected from** A, B, C **and** D. Since the phrase "selected from" is used, the group from which selection is made includes A, B, C, **and** D. This form is entirely proper, and the objection to the alternative language should be withdrawn.

B. Response to the Rejection of the Claims under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

The Advisory Action maintained the Enablement Requirement of 35 U.S.C. § 112, first paragraph. As noted previously while the Office has acknowledged that the claims adequately describe how to make and use the compounds of Formula (Ia) and pharmaceutically acceptable salts thereof, the Office disputes that the specification reasonably provides enablement for making "any hydrates or solvates within the scope of ... claim 1."

The only evidence cited in support of the rejection is the Vippagunta reference which allegedly states that "prediction of the formation of solvates or hydrates of a compound is complex or difficult." Advisory Action at p. 2.

Applicants respectfully request reconsideration of the Office's position that the person skilled in the art would not be able to make hydrates and solvates of the compounds of formula (Ia) without undue experimentation. Applicants respectfully submit that the Office's position is unsupported by any substantial evidence of record and is inconsistent with the weight of evidence that has been cited in the application.

In addition, Applicants respectfully submit that the recent **Final Decision of the Board of Patent Appeals and Interferences** in *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647 (Bd. Pat. App. & Int., Sept. 15, 2010) (available online at http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd2009015302-09-15-2010-1) in which the Board (Administrative Patent Judges Scheiner, Green and Prats) reversed an Examiner's rejection of claims directed to a compound "... or pharmaceutically acceptable solvate thereof" also compels withdrawal of the same rejection made in the present application. Applicants attach a copy of the Board's Final Decision in that case, one which explicitly discusses the question of enablement of a claim that is directed to a "compound ... or ... solvate thereof" when no working examples of any solvates was provided in the specification.

A similar conclusion was reached by the Board in the **Final Decision of the Board of Patent Appeals and Interferences** in *Ex Parte Germeyer*, Appeal No. 2010-005038, Appln. No. 10/891,554 (Bd. Pat. App. & Int., November 30, 2010) (available online at http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd2010005038-12-01-2010-1). In this Decision, the Board (Administrative Patent Judges Grimes, Fredman and Walsh) reversed an Examiner's rejections made under the enablement and written description requirements of 35 U.S.C. § 112, first paragraph, for "lacking enablement for hydrates of ... compounds and hydrates of steroids" and for lacking adequate written description of hydrates.

Applicants note that in the above referenced decisions of the Board of Patent Appeals and Interferences, six out of the ten Administrative Patent Judges of the Biotechnology Section of the Board have subscribed to Final Decisions reversing the type of rejection the Examiner has maintained here.

The burden is not on the Applicants to prove that their claims are enabled, but, instead, in order to reject the claims for lack of enablement, the burden is upon the Office to show that the claims are not enabled. It is not incumbent upon Applicants to provide proof that their compounds can form solvates or hydrates by providing working examples of solvates or hydrates when the Office has provided no evidence to the contrary. As the Board in *Ex Parte Liu* explained:

> "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." *In re Armbruster*, 512 F.2d 676, 678 (CCPA 1975). Instead, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).
>
> Thus, the threshold issue raised by this rejection is not whether Appellants have established that their Specification is enabling for making ... solvates of the compound of Formula I. Rather, the issue is whether the Examiner has met his initial burden of providing a reasonable explanation as to why it isn't.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 7 (Bd. Pat. App. & Int., Sept. 15, 2010).

Applicants note that the reasons given by the Examiner in making the enablement rejection are precisely the same as those given by the Examiner in *Ex Parte Liu*, reasons that the Board in *Ex Parte Liu* found insufficient to support an enablement rejection.

The Examiner argues that the claims are inadequately enabled because Applicants' specification allegedly does not describe a working example in which a hydrate or solvate is formed.

In response to this argument, Applicants have pointed out that there is *no evidence whatsoever* of record to suggest that hydrates or solvates of compounds of the presently claimed compounds could not be made.

The Examiner has not pointed to any evidence that the inventors prepared any of the examples under conditions that would be favorable for forming hydrates or solvates. Vippagunta points out (see p. 4 col. 2 to p. 5 col. 1 of Vippagunta), that investigation of solid state forms such as hydrates and solvates is important during clinical development to obtain regulatory approval of a drug candidate. The examples of the present application, in contrast, were

performed earlier in the drug development process – during drug discovery – when the focus is on optimizing the pharmacological activity of the compounds and the formation of different solid state forms is not a concern. The methods usually used for purification of compounds in drug discovery, as described in the examples (typically by chromatography followed by evaporation of the product-containing fractions under reduced pressure) do not involve crystallization under the conditions favorable to forming hydrates and solvates.

The Examiner has also not pointed to any evidence showing that compounds of the working examples were not actually formed as hydrates or solvates. The Office has not provided any evidence that the compounds of the examples were not formed as hydrates or solvates, or any evidence that if the example compounds had been obtained in the form of a hydrate or solvate that the inventors would have detected the fact that the compounds were solvates. Routine characterization of compounds in the drug discovery process – typically by ^{1}H NMR and mass spectrometry – focuses on confirming that the compound has been formed, and the medicinal chemist does not typically attempt to identify whether the compound is present in the form of a solvate. The specification clearly explains that samples for NMR and mass spectrometry were analyzed *in solution* not in the solid state. *See* Specification p. 127. Hydrates and solvates, by definition, only exist in the solid state. Furthermore, when organic chemistry researchers see peaks in the NMR spectrum of organic compounds that are attributable to water or solvents used in the preparation or purification of such compounds, such peaks are disregarded as being due to solvent impurities in the organic compound. *See* Gottlieb, et al., *J. Org. Chem.* **1997**, *62*, 7512-7515 (copy attached). Thus, the fact that the specification does not explicitly state whether compounds of the invention were isolated in the form of hydrates or solvates does not indicate in any way that the example compounds failed to form solvates, that compounds of the invention did not or would not be capable of forming hydrates or solvates, or that the person skilled in the art would have any difficulty making such hydrates or solvates from compounds of the invention.

The Board in *Ex Parte Liu* also found the Examiner's reasoning that solvates were not enabled because of a lack of working examples to be unconvincing because the "conditions ... were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates." *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 9 (Bd.

Pat. App. & Int., Sept. 15, 2010). In the present case Applicants have pointed out that not only were the conditions unfavorable for hydrate or solvate formation, but that no attempt was made to detect whether the compounds were present in the form of hydrates or solvates. The Examiner has presented no contrary evidence showing that the conditions would have been favorable for hydrate or solvate formation or that the analytical methods used by Applicants would have detected a hydrate or solvate, if present.

A further argument made by the Examiner is that the claims are inadequately enabled because it is allegedly difficult to predict whether solvates would form, citing Vippagunta as evidence thereof.

Applicants have provided evidence that even if solvate formation is unpredictable, this fact should not lead to a finding of lack of enablement because hydrates and solvates can be prepared using routine methods. The evidence cited by the Applicants has indicated that even if *predicting* solvate formation is difficult, *making and detecting* the compounds which form hydrates and solvates *empirically* is easy, simple, requires few steps, and demands little time, and that the person of skill in the art routinely engages in such experimentation, and that the techniques for performing such experimentation are well known. The evidence cited by the Applicants demonstrates that to make hydrates and solvates, samples of the organic compound are simply exposed to water or various different solvents. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. Other typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999. The evidence cited by the Applicants shows that once hydrates and solvates are formed, they can be readily analyzed by routine methods. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of solvate molecules in the sample. As evidence thereof, see page 18, right column, Vippagunta. Applicants have

also cited evidence that solvate and hydrate form is so routine as to be amenable to high throughput crystallization as described, for example, in Morissette, *et al.*, *Adv. Drug Delivery Rev.*, **2004**, *56*, 275-300. Thus, formation of hydrates and solvates requires no more than routine screening.

Applicants note that the Board in *Ex Parte Liu* also considered the alleged unpredictability of solvate formation and its effect on the question of enablement of claims that recite a "compound ... or ... solvate thereof." The Board included in its Final Decision a discussion of the Vippagunta reference cited by the Examiner. The Examiner in the *Liu* case (Examiner Rao) had apparently made the same arguments with respect to Vippagunta the Examiner makes here. The Board did not dispute that "[the] Vippagunta reference[] show[s] that it is difficult to predict whether a given compound will form a solvate or hydrate" *Ex Parte Liu*, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 9 (Bd. Pat. App. & Int., Sept. 15, 2010). However, the Board rejected Examiner Rao's argument that the claims should be found to be insufficiently enabled as the result of such unpredictability because "the reference[] also provide[s] evidence that solvates and hydrates are routinely produced and characterized empirically." *Id.*

The Board in *Ex Parte Liu* therefore disagreed with the position that the Examiner has taken in the present application that the alleged unpredictability of solvate formation should be found dispositive on the question of enablement. Instead, based on the Vippagunta references which is also of record in the present application, the Board agreed with the present Applicants' position that the ease and routineness of the methods available for hydrate and solvate formation heavily outweigh any unpredictability that might be involved.

Despite the fact that the burden is upon the Office to show lack of enablement, in Applicant's previous responses, Applicants have cited the following documents as providing **evidence** supporting enablement of Applicants' claims.

- Vippagunta, et al., *Adv. Drug Delivery Reviews*, **2001**, 48, 3-26.
- Morisette, et al., *Adv. Drug Delivery Reviews*, **2004**, 56, 275-300.

- Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999.
- Sigma-Aldrich catalog entries for commercially available pyrimidine hydrates, namely 4,6-diamino-2-mercaptopyrimidine hydrate (catalog no. 125830); 2-amino-6-chloro-4-pyrimidinol hydrate (catalog no. 07460); 2-amino-6-hydroxy-2-mercaptopyrimidine monohydrate (catalog no. A57406); and 4,5-diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate salt hydrate (392464).
- Abstract of Quesada, et al, *Acta Cryst*, 2003, C59, 102-104, documenting 2-amino-5-nitro-4,6-dipiperidinopyrimidinium hydrogensulfate monohydrate.

The Office, in contrast, has pointed to **no evidence** that shows that hydrates and solvates of the presently claimed compounds do not exist or could not be made.

The evidence of record shows the following:

- The claims are drawn to compounds of Formula (Ia), and pharmaceutically acceptable salts, hydrates and solvates thereof.
- The Office does not dispute, and, in fact, by withdrawing some of the grounds of rejection for lack of enablement, has acknowledged that it would not involve undue experimentation to make compounds of Formula (Ia), and pharmaceutically acceptable salts thereof. The only dispute is whether it would involve undue experimentation to make hydrates and solvates of the claimed compounds.
- Vippagunta on p. 15 indicates that it has been estimated that "approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates." Vippagunta also indicates that solvates are similar to hydrates. Thus the person skilled in the art would recognize that a substantial percentage of pharmaceutically active substances are capable of forming hydrates and solvates.
- Applicants provided over 300 Examples of compound of the invention in the specification. The specification does not indicate whether or not these compounds were obtained in the form of hydrates. However, it is not customary in early drug discovery to attempt to form hydrates or solvates or to analyze compounds to evaluate whether they

are present as hydrates are solvates, as polymorphism and solvate or hydrate formation is usually investigated in later stages of drug development as a drug candidate is being advanced towards regulatory approval. *See* Vippagunta pp 4-5. The compounds of the present application were analyzed in solution by NMR and LCMS and not by the solid phase testing techniques which would detect solvates and hydrates. The evidence indicates, however, that about one third of pharmaceutically active substances are capable of forming hydrates.

- There is no evidence of record showing that the compounds of Formula (Ia), which are pyrimidines, would be incapable of forming hydrates or solvates.
- Applicants have provided evidence that pyrimidines are known to exist in the form of hydrates. Evidence of five examples of such compounds was provided. These literature compounds share a common core structure (i.e. pyrimidine) with the claimed compounds of Formula (Ia). This evidence includes Sigma-Aldrich catalog entries for four such compounds that are commercially available, namely 4,6-diamino-2-mercaptopyrimidine hydrate (catalog no. 125830); 2-amino-6-chloro-4-pyrimidinol hydrate (catalog no. 07460); 2-amino-6-hydroxy-2-mercaptopyrimidine monohydrate (catalog no. A57406); and 4,5-diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate salt hydrate (392464), in addition to 2-amino-5-nitro-4,6-dipiperidinopyrimidinium hydrogensulfate monohydrate, which is described in the abstract of Quesada, et al, *Acta Cryst*, 2003, C59, 102-104.
- Applicants have cited evidence that formation of hydrates and solvates generally is straightforward, involves no more than routine experimentation, and that the person skilled in the art typically engages in such experimentation. Typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999. Once hydrates and solvates are formed they can be analyzed by routine methods as described, for example, in Vippagunta, p. 18 to detect and quantify the presence of solvate molecules in the sample. The experimentation involved is so

routine that it can be applied in high-throughput methods as described, for example, in Morissette, *et al.*, *Adv. Drug Delivery Rev.*, **2004**, *56*, 275-300.

Applicants submit that the above facts present a factual situation with respect to enablement of hydrates and solvates which is no less favorable in any material respect to the situation that was presented to the Board of Patent Appeals and Interferences in *Ex Parte Liu.*

In *Ex Parte Liu*, the Board explained that the burden is on the Examiner to show why solvates were not adequately enabled.

> Thus, the threshold issue raised by this rejection is not whether Appellants have established that their Specification is enabling for making ... solvates of the compound of Formula I. Rather, the issue is whether the Examiner has met his initial burden of providing a reasonable explanation as to why it isn't.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 7 (Bd. Pat. App. & Int., Sept. 15, 2010).

The Vippagunta reference cited by Examiner Rao in *Ex Parte Liu* was the same as the Vippagunta reference the Examiner cites in the present application. The Board in *Ex Parte Liu* concluded that the evidence was insufficient to establish that Liu's claims drawn to a "compound ... or ... pharmaceutically acceptable salt thereof" were inadequately enabled. The Board explained:

> [W]hile the ... Vippagunta reference[] show[s] that it is difficult to predict whether a given compound will form a solvate or hydrate, or what its composition will be, the references also provide evidence that solvates and hydrates are routinely produced and characterized empirically.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 8 (Bd. Pat. App. & Int., Sept. 15, 2010).

With respect to the lack of working examples, the Examiner has not shown that compounds of the invention were made under conditions which would have been favorable for solvent formation. In addition, there is no information showing that the Examples were not formed as hydrates or solvates: the compounds were analyzed in solution, not in the solid phase. The same situation prevailed in *Ex Parte Liu*:

> [The] conditions . . . were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 9 (Bd. Pat. App. & Int., Sept. 15, 2010).

The Board in *Ex Parte Liu* decided that a lack of working examples of solvates was insufficient to demonstrate lack of enablement of Liu's claims drawn to a "compound ... or ... solvate thereof" because it would not have required more than routine empirical experimentation to make solvates, notwithstanding the fact that predicting solvent formation in advance might be challenging. The Board explained:

> Essentially, we agree with Appellants that the Examiner has overemphasized the importance of working examples and given too little credit to the abilities of a person having ordinary skill in the art.

Ex Parte Liu, Appeal No. 2009015302, Appln. No. 10/820,647, Slip Op. at p. 8 (Bd. Pat. App. & Int., Sept. 15, 2010) (citations omitted).

The same situation is present in this application. The Examiner has overemphasized the fact that the specification does not describe that compounds of the invention were prepared in the form of hydrates or solvates and that it is difficult to predict *formation* of hydrates and solvates in advance while disregarding the fact that hydrates and solvates of pharmaceutical compounds are ubiquitous and can be prepared by the person skilled in the art using nothing more than routine empirical experimentation. Here too "the Examiner has overemphasized the importance of working examples and given too little credit to the abilities of a person having ordinary skill in the art."

If the enablement rejection is not to be withdrawn, Applicants request that the Examiner, in order to clarify the record as to the reasons why the rejection is being maintained, issue a further Office Action explaining what are the legally significant factual differences between the situation which was presented to the Board by *Liu* and the situation presented by the present application, and why the differences justify maintaining the enablement rejection in the present application. Applicants note that the same reasoning supported by the same references has been employed in the present Application as in the Application in *Liu*, where the rejection was found by the Board to have been made in error. Alternatively, if the Examiner cannot identify any legally significant differences justifying maintaining the rejection, Applicants invite the Examiner to explain what was the mistake the Examiner considers Administrative Patent Judges

Scheiner, Green and Prats made in the *Liu* decision reversing Examiner Rao's identically reasoned rejection in Application 10/820,647.

Applicants note that the Office Action dated May 13, 2010 was issued prior to the Board's decision in *Liu*, and was therefore prepared by Examiner Murray without the benefit of the insight the *Liu* decision provides as to the proper legal standards to be applied when considering enablement of compound claims that refer to a solvate, and the Board's view of the sufficiency of a rejection based on exactly the same reasoning as the one made in the present application.

In view of all the foregoing remarks, the Applicants respectfully request that the rejection of claims under the enablement requirement of 35 U.S.C. § 112, first paragraph, be withdrawn.

No fee is believed to be due. However, the Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050 quoting Attorney's Docket No. 20750-0007US1 / 034.US5.PCT.

Respectfully submitted,

Date: January 5, 2011

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEVIN LIU and CUNXIANG ZHAO

Appeal 2009-015302
Application 10/820,647
Technology Center 1600

Before TONI R. SCHEINER, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-13, 18-36, 41-49, 51-57, and 59-69, directed to a pharmaceutical compound and methods of using it. The claims have been rejected as lacking enablement. We have jurisdiction under 35 U.S.C. § 6(b).

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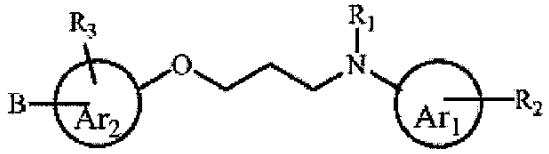
[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

"[T]he present invention relates to aryl compounds and methods for treating various diseases by modulation of nuclear receptor mediated processes . . . in particular processes mediated by peroxisome proliferator activated receptors (PPARs)" (Spec. 1).

Representative claim 1 is directed to an aryl compound having the structure of Formula I:

(I) 

wherein [Ar_1, Ar_2, R_1, R_2, R_3, B, and R_4 are as detailed on page 25 of Appellant's Brief on Appeal, in the Claims Appendix],

"or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof."

Representative claim 51 reads: "A method of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR with a compound of Claim 1 and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner."

Representative claim 59 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient."

Finally, representative claim 60 reads: "A method of treating a metabolic disorder or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient."

The Examiner rejected the claims as follows:[2]

(A) Claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 under the first paragraph of 35 U.S.C. § 112 "because the specification, while being enabling for a compound of Formula I or a pharmaceutically acceptable N-oxide or salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable **prodrug, metabolite, ester, amide** or **solvate** thereof" (Ans. 4); and

(B) claims 51-57 and 59-65 under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for a method for treatment of diabetes, does not reasonably provide enablement" for the various methods recited in these claims (*id.* at 10).

We reverse.

ENABLEMENT REJECTION A

Findings of Fact

1. The Examiner rejected claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 "because the specification, while being enabling for a compound of Formula I or . . . [an] N-oxide or salt thereof does not reasonably provide enablement for a pharmaceutically acceptable **prodrug, metabolite, ester, amide** or **solvate** thereof" (Ans. 4).

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[2] Claims 50 and 70 have been allowed (Final Rej., October 4, 2007). Claims 14-16, 37-40, and 58 have been cancelled (App. Br. 3).

2. The Specification teaches that an amide is "a chemical moiety with formula -C(O)NHR or -NHC(O)R, where R is optionally substituted" and "[a]ny amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be amidified" (Spec. 13).

3. "The procedures and specific groups to be used to . . . make[ ] such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., . . . 1999, which is incorporated herein by reference" (Spec. 13).

4. The Specification defines a prodrug as "an agent that is converted into the parent drug *in vivo*" (Spec. 27).

> An example . . . would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

(*Id.*)

5. The Specification teaches that "the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like" (Spec. 19).

6. West,[3] a reference cited by the Examiner, teaches that

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[3] ANTHONY R. WEST, SOLID STATE CHEMISTRY AND ITS APPLICATIONS 358, 365 (1988).

> The factors that govern whether or not solid solutions [i.e., hydrates and solvates], especially the more complex ones, form are understood only qualitatively. For a given system, it is not usually possible to predict whether solid 'solutions' will form or, if they do form, what is their compositional extent. Instead, this has to be determined experimentally.

(West 365.)

7. Vippagunta,[4] another reference cited by the Examiner, teaches:

> Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates.

(Vippagunta 18.)

Discussion

The Examiner acknowledges that "[t]he term 'prodrug' [is] generally known to represent 'a physiologically functional derivative, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the invention or an active metabolite thereof'" (Ans. 4-5). In addition, the Examiner acknowledges

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[4] Sudha R. Vippagunta et al., *Crystalline solids*, 48 ADVANCED DRUG DELIVERY REVIEWS 3-26 (2001).

that "many strategies for making prodrugs" were known in the art at the time of the invention (*id.* at 6).

However, the Examiner concludes that the Specification is not enabling for prodrugs or pharmaceutically active metabolites of the compound of Formula I because "[t]he term 'prodrug and/or 'metabolite' is directed to esters and amides of compounds of Formula I" (*id.* at 5), but the "substituent groups in Formula I already include . . . acids, esters, amides, etc." (*id.*), and "[t]he specification does not provide what other 'compounds' . . . are intended to be the above refer[enc]ed 'prodrugs' and 'metabolites'" (*id.*). In other words, because the Specification doesn't provide examples of other amide or ester derivatives of the compound of Formula I capable of functioning as prodrugs or pharmaceutically active metabolites, the Examiner concludes "[i]n a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a 'prodrug'" or metabolite (*id.* at 6).

In addition, the Examiner concludes that "[t]he quantity of experimentation needed [to make solvates of the compound of Formula I] would be an undue burden on [one] skilled in the chemical art" (*id.* at 10) because "[t]he state of the art is that [it] is not predictable whether solvates will form or what their composition will be" (*id.* at 7). The Examiner notes that "some of the exemplified compounds within the claimed genus were in contact with solvent . . . [but] have not formed solvate" (*id.* at 6), thus, "[t]here is no evidence that solvates of these compounds actually exist" (*id.* at 9).

Nevertheless,

> [T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by . . . [a] claim is not adequately enabled by the description of the invention provided in the specification . . . this includes . . . providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.

In re Wright, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993).

In other words, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." *In re Armbruster*, 512 F.2d 676, 678 (CCPA 1975). Instead, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

Thus, the threshold issue raised by this rejection is not whether Appellants have established that their Specification is enabling for making prodrugs, pharmaceutically active metabolites, esters, amides or solvates of the compound of Formula I. Rather, the issue is whether the Examiner has met his initial burden of providing a reasonable explanation as to why it isn't.

The Examiner's explanation as to why it would have required undue experimentation for one skilled in the art to make and/or use prodrugs, metabolites, esters, amides or solvates of the compound of Formula I is insufficient to satisfy that initial burden.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art . . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Forman, 230 USPQ 546, 547 (BPAI 1986). "The key word is 'undue,' not 'experimentation.'" *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).

Essentially, we agree with Appellants that the Examiner has overemphasized the importance of working examples (App. Br. 10), and given "too little credit to the abilities of a person having ordinary skill in the art" (*id.* at 11).

Even accepting that the experimentation required to produce prodrugs and metabolites based on the compound of Formula I would be tedious and time-consuming, the Examiner has not established that it would have been anything other than routine and empirical for one of skill in the art.

In addition, while the West and Vippagunta references show that it is difficult to predict whether a given compound will form a solvate or hydrate, or what its composition will be, the references also provide evidence that solvates and hydrates are routinely produced and characterized empirically (FF 6, 7). As for the Examiner's concern that some of the compounds of the invention were in contact with solvents, but didn't form solvates (Ans. 6), Appellants point out that the examples in the Specification used "a drying agent . . . to remove trace amounts of water as part of the purification

process following a number of the chemical steps involved in the syntheses of exemplary compounds" (App. Br. 14), thus, "conditions . . . were unfavorable for solvate formation and therefore not indicative of the nonexistence of solvates" (*id.* at 14-15).

Conclusion

The Examiner has failed to provide a reasonable explanation as to why pharmaceutically acceptable prodrugs, metabolites, esters, amides or solvates of Formula I are not adequately enabled by the description of the invention provided in the Specification.

ENABLEMENT REJECTION B

Findings of Fact

8. The Examiner concedes that the Specification is enabling for a method of treating diabetes, but maintains the rejection of claims 51-57 and 59-65 because

> [T]he specification . . . does not reasonably provide enablement for a method of modulating a peroxisome proliferator[]-activated receptor (PPAR) function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a disease generally; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally.

(Ans. 10.)

9. According to the Specification:

> Biological processes modulated by PPAR . . . include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia . . . , macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte formation.

(Spec. 1-2.)

10. The Specification teaches that "[s]ubtypes of PPAR include PPAR-alpha, PPAR-delta (also known as . . . PPAR-beta . . .) and two isoforms of PPAR-gamma" (Spec. 2). All of the isoforms "have been shown to be important molecular targets for treatment of metabolic and other diseases" (*id.* at 3), and "[c]ompounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models" (*id.* at 1).

11. According to the Specification, activators of PPAR-gamma "have been clinically shown to enhance insulin-action, to reduce serum glucose and to have small but significant effects on reducing serum triglyceride levels in patients with Type 2 diabetes" (Spec. 2); and "have been implicated in the treatment of polycystic ovary syndrome" (*id.* at 24).

12. "Pharmacological PPAR-alpha activators . . . are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity" and "may be useful in treating atherosclerotic diseases" (Spec. 24-25).

13. "PPAR-delta . . . has been shown to be a valuable molecular target for treatment of dyslipedimia [sic] and other diseases" (Spec. 2).

14. The Specification teaches that

> [T]he disease to be treated by the methods of the present invention is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

(Spec. 25.)

15. According to the Specification:

> The term "modulate" refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the activity of a PPAR. The term "modulate" also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner.

(Spec. 20-21.)

16. The Specification teaches that "[c]ompounds may be screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR [α, γ, and δ] subtypes" (Spec. 22). Eighteen "compounds were evaluated in a cell-based [transfection] assay to determine their human PPAR [α, γ, and δ] activity" (Spec. 48). The results, displayed in the Table on pages 49-51 of the Specification, show that most of the compounds tested were able to activate two or more PPAR subtypes under experimental conditions, while a few compounds were unable to activate any subtype at all.

17. Fayer,[5] a reference cited by the Examiner, teaches that there is a "[l]ack of correlation between in vitro inhibition of CYP3A-mediated metabolism by [RG 12525] a PPAR-gamma agonist and its effect on the clinical pharmacokinetics of midazolam, an in vivo probe of CYP3A

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[5] JL Fayer et al., *Lack of correlation between in vitro inhibition of CYP3A-mediated metabolism by a PPAR-gamma agonist and its effect on the clinical pharmacokinetics of midazolam, an in vivo probe of CYP3A activity*, 41 J. CLIN. PHARMACOL. 305-316 (2001) (Abstract only).

activity," probably due to "the high degree of RG 12525 protein binding" (Fayer, Abstract). Fayer emphasizes "the need to recognize factors other than plasma drug concentrations and potency of in vitro enzyme inhibition when extrapolating in vitro data to predict in vivo drug-drug interactions" (*id.*).

Discussion

The threshold issue raised by this rejection is whether the Examiner has met his initial burden of providing a reasonable explanation as to why the Specification isn't enabling for using the compounds of Formula I to modulate a PPAR function, treat a PPAR-modulated disease or condition, inhibit the formation of adipocytes, treat a metabolic disorder, or treat a variety of specifically identified diseases.

With respect to claims 51 and 52, directed to "modulating a PPAR function," the Examiner argues that modulating "generally encompasses blocking, activating, partial blocking and partial activating. However, the compounds were not shown to have all these properties . . . [and] it is revolutionary for a compound to be effective as a blocker, activator and partial blocker/activator" (Ans. 11).

However, the Examiner's interpretation of the term "modulating" doesn't comport with the Specification's definition of the term (FF15). We agree with Appellants that "nowhere in the specification is it suggested that any of the claimed compounds have the ability to block, activate partially block and partially activate a PPAR function at the same time" (App. Br. 18).

With respect to the remaining claims, the Examiner finds that "one having ordinary skill in the art would have to undergo an undue amount of

experimentation to use the claimed compounds as PPAR regulators" (Ans. 11), because PPAR activity "is highly structure specific and unpredictable as can be seen from the range of the results obtained for the tested compounds" (*id.* at 10-11).

However, the "range of results" obtained for the 18 compounds tested simply reflects the fact that most of the compounds were able to activate two or more PPAR subtypes, while a few were unable to activate any subtype at all (FF16). The Specification teaches, and the Examiner does not dispute, that all of the isoforms "have been shown to be important molecular targets for treatment of metabolic and other diseases" (Spec. 3; FF10) - so it's not clear why structure specificity would be a problem, especially as the Specification discloses an assay for determining subtype specificity.

The Examiner also argues that "there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR" (Ans. 11). The Examiner cites Fayer as evidence that "such correlation or lack thereof is important to predict drug-drug interactions" (*id.*), but doesn't elaborate further.

Again, it is the Examiner's initial burden to "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Marzocchi*, 439 F.2d at 224. The Examiner has not done so.

Finally, the Examiner acknowledges that the Specification "provides a select list of disorders such as diabetes, hyperinsulinemia, atherosclerosis, etc." (Ans. 12) to be treated with the compounds of Formula I, but argues

that "[c]laims are drawn to a method for treatment of 'a PPAR-modulated disease or condition' . . . include[ ] disorders that are known to exist and those that may be discovered in the future and therefore, [are] extremely broad" (*id.*).

Nevertheless, it is well settled that the purpose of the Specification is not to "enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004).

Conclusions

The Examiner has failed to meet the initial burden of providing a reasonable explanation as to why the Specification isn't enabling for using the compounds of Formula I to modulate a PPAR function, treat a PPAR-modulated disease or condition, inhibit the formation of adipocytes, treat a metabolic disorder, or treat a variety of specifically identified diseases.

SUMMARY

(A) The rejection of claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 under the enablement provision of 35 U.S.C. § 112, first paragraph, is reversed.

(B) The rejection of claims 51-57 and 59-65 under the enablement provision of 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

cdc

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SABINE GERMEYER, CHRISTOPHER JOHN MONTAGUE MEADE, HELMUT MEISSNER, GERD MORSCHHAEUSER, MICHEL PAIRET, SABINE PESTEL, MICHAEL P. PIEPER, GERALD POHL, RICHARD REICHL, and GEORG SPECK

Appeal 2010-005038
Application 10/891,554
Technology Center 1600

Before ERIC GRIMES, JEFFREY N. FREDMAN, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to a propellant-free inhalable solution or suspension, a pharmaceutical

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

composition, a method of treating allergic rhinitis, and a kit. The Patent Examiner rejected the claims on multiple grounds: lack of written description, lack of enablement, indefiniteness, anticipation, and nonstatutory obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

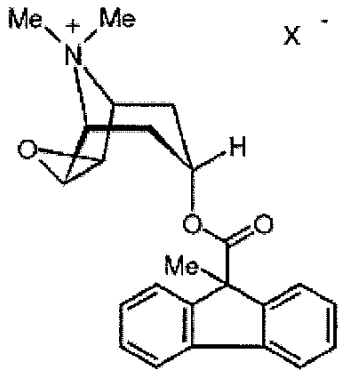
STATEMENT OF THE CASE

Claims 1, 3, 5-8, 26-30, 32-36, 38-40 and 45-48 are pending. Appellants request clarification concerning claims 33, 34, and 38, which Appellants say were listed as withdrawn from consideration, but were also listed as rejected. (App. Br. 2, citing Final Rej.) The Examiner's Answer clarifies that "claims 33-34 and 38 are withdrawn from consideration" (Ans. 2), and they are no longer listed in rejections. Accordingly, the claims on appeal are claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48.

The invention relates to compositions said to be useful in treating respiratory complaints. (Spec. 1, ll. 10-12.) The compositions are described as based on steroids and salts of an anticholinergic of formula **1**. (*Id.* at ll. 19-25.) Claim 1 is illustrative of the subject matter:

1. A propellent-free inhalable solution or suspension comprising:

(a) a compound of formula 1



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wherein X is an anion with a single negative charge or an enantiomer, mixtures of enantiomers, racemate or hydrate thereof; and

(b) a steroid, selected from the group consisting of methyl prednisolone, prednisone, butixocort propionate, RPR-106541, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126, dexamethasone, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-l l β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17βcarbothioic acid (*S*)-fluoromethyl ester, and 6α,9α-difluoro-l lβ-hydroxy-l6α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioic acid (*S*)-(2-oxo-tetrahydrofuran-3*S*-yl) ester, and an enantiomer, racemate, pharmacologically acceptable acid addition salt, hydrate, and mixture thereof.

The Examiner rejected the claims as follows:

- claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement to the extent the claims include hydrates of formula 1 compounds and hydrates of steroids (Ans. 4-7);
- claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, first paragraph, as lacking enablement for hydrates of formula 1 compounds and hydrates of steroids (*id.* at 7-10);

• claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, second paragraph, as the term "derivative" is indefinite (*id.* at 11);

• claims 1, 3, 5-8, 26-30, 32, 35, 36,[2] 39, 40 and 45-48 under 35 U.S.C. § 102(e) as anticipated by Germeyer[3] (*id.* at 12-14); and

• claims 1, 3, 5-8, 30 and 40, provisionally, on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 11-13 and 17 of copending Application No. 11/182,382 in view of Germeyer (*id.* at 15-16).

WRITTEN DESCRIPTION and ENABLEMENT

The Issues

Concerning written description, the Examiner's position is that (i) "hydrates" of the compounds of formula 1, and (ii) "hydrates" of steroids, were not described in such a way as to convey that Applicants had possession of the invention at the time the Application was filed. (Ans. 4.) Concerning enablement, the Examiner's position is that the Specification does not reasonably provide enablement for compositions or kits comprising hydrates of compounds of formula I or of steroids. (Ans. 7.)

The two rejections thus focus on whether "hydrates" were adequately described or enabled, respectively. Because facts used in deciding these questions are common to both rejections, we will review them together. *Cf. LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336,

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[2] A typo in the Answer included canceled claim 37 in the rejection under § 102(e).

[3] US 6,790,856 B2, issued to Sabine Germeyer et al., Sep. 14, 2004.

1345 (Fed. Cir. 2005) (observing that although written description and enablement are separate requirements, they "usually rise and fall together").

The principles guiding review are:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *LizardTech*, 424 F.3d at 1345).

Analysis

The Examiner focuses on the difficulty of predicting hydrate structures, citing Vippagunta,[4] Braga,[5] and Seddon[6] as evidence that predicting hydrate structure is difficult.

Appellants cite to a Chemical Dictionary,[7] and to Hilfiker,[8] as evidence that hydrates form whether their structure is known in advance or

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[4] Sudha R. Vippagunta et al., *Crystalline solids*, 48 ADVANCED DRUG DELIVERY REVIEWS 3-26 (2001).
[5] Dario Braga et al., *Making crystals from crystals: a green route to crystal engineering and polymorphism*, CHEM. COMMUN. 3635-3645 (2005).
[6] Kenneth R. Seddon, Pseudo*polymorph: A Polemic*, 4 CRYSTAL GROWTH & DESIGN 1087 (2004).
[7] Richard J. Lewis, Sr., HAWLEY'S CONDENSED CHEMICAL DICTIONARY, 14th ed., 581 (John Wiley & Sons, Inc., New York 2001).

not. Appellants also argue that passages in Vippagunta support finding that hydrates form whether hydrate structural information is available in advance or not, and that Vippagunta thus shows the Examiner's concerns are misdirected.

We think that Appellants have the better position. The claims include using whatever hydrate of formula 1 or a steroid is available, and do not require a hydrate having a specific structure, and do not require that a hydrate structure must be identified. Vippagunta, Braga, and Hilfiker evidence that hydrates form naturally, whether their structures can be predicted in advance or not. We have reviewed Seddon but give it little weight because it is directed to semantics, not the issues in this appeal. We therefore agree with Appellants that the rejection's focus on predicting hydrate structure is misdirected. Further, the rejection provides no evidence that a hydrate cannot be used until its structure is determined. We find the evidence relied on for the rejections insufficient to carry the burden of showing that a person of ordinary skill in the art (1) would not credit Appellants with possession of hydrate embodiments of the invention, or (2) would require undue experimentation to make and use hydrate embodiments of the invention.

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[8] R. Hilfiker et al., *Polymorphism – Integrated Approach From High-Throughput Screening To Crystallization Optimization*, 73 J. THERMAL ANALYSIS AND CALORIMETRY 429-440 (2003).

DEFINITENESS

The Issue

The Examiner finds that (1) "[c]laims 5-6 explicitly refer to derivatives of the specific steroids recited in said claims," and (2) "Appellants' specification in paragraph [0017] defines any mention of steroids to also include reference to derivatives thereof." (Ans. 11.) The Examiner further finds that the meaning of "derivative" is unknown because (1) the Specification "does not define what constitutes a derivative of steroids in general or [of] the specific steroids recited in Appellants' claims 5-6, for example," and (2) the ordinary dictionary meaning ("a chemical substance related structurally to another substance and theoretically derivable from it") "does not shed light on what Appellants[] intended for the meaning of a derivative of any of the specific steroids recited in Appellants' claim 6." (Ans. 11.) The Examiner concludes that the claims are indefinite.

Appellants contend that because they amended the claims to delete the word "derivative," that particular subject matter is no longer included in the literal claim meaning, and the rejection should thus be reversed. (App. Br. 16.)

Principle of Law

"A claim is indefinite if its legal scope is not clear enough that a person of ordinary skill in the art could determine whether a particular composition infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

Analysis

Claim 5 defines a solution or suspension in which any one of the steroids listed in claim 1 is in one of ten named salt forms, or a mixture thereof. Claim 6 defines a solution or suspension in which any one of the steroids listed in claim 1 is a salt. Neither claim uses the term "derivative." Thus we disagree with the Examiner's statement that "[c]laims 5-6 explicitly refer to derivatives." If the rejection were based only on the face of the claims, we would conclude that neither claim is indefinite on its face. The rejection, however, is also based on a finding that the Specification defined the word "steroid" to include derivatives.

The Specification states:

> [a]ny reference to steroids **2** within the scope of the present invention includes a reference to the salts or derivatives which may be formed from the steroids. Examples of possible salts or derivatives include: [list of ten particular salt forms].

(Spec. 4, ll. 13-16.) The rejection gives little weight to the examples, and the Examiner argues that examples are not definitions. (Ans. 11.)

The rejection effectively concludes that a person of ordinary skill in the art would not find the Specification sufficiently informative for understanding the claims. To understand the claims, the rejection discounts the examples and instead gives more substantial weight to the purported failure of a general dictionary to shed light on what Appellants intended. We disagree with that approach. "[T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see also, Toro Co. v. White Consolidated Inds.*, 199 F.3d 1295, 1301 (Fed. Cir. 1999) (claim

terms are "not construed in a lexicographic vacuum, but in the context of the specification and drawings").

We think that a person of ordinary skill in the art would find the Specification's list of examples instructive of the kinds of salts or derivatives intended. We conclude that a person of ordinary skill in the art could determine whether a particular composition infringes the claims or not.

ANTICIPATION

The Issue

The Examiner's position is that Germeyer disclosed a composition comprising a compound of formula 1 in combination with a steroid, to be administered by inhalation. The Examiner cited evidence said to show that Germeyer described a propellant-free inhalable solution or suspension, a pharmaceutical composition, a method of treating allergic rhinitis, and a kit, all as defined by Appellants' claims.

Appellants contend that "[t]he rejection is made based on choosing parts from different, separate embodiments disclosed in Germeyer and selectively combining these separate teachings to piece together a fictitious embodiment – not actually disclosed by the reference – to allegedly meet the elements of the instant claims on appeal." (App. Br. 17.) Appellants state that "Germeyer does disclose appellants' specific compound of formula **1** in preparation Example 6 (cols. 11-12). But this does not provide a disclosure of a composition embodiment which contains this compound and meets the other elements of the claims on appeal." (*Id.*) More specifically, Appellants argue that "Germeyer fails to disclose any specific embodiment of a

composition containing one of the specific betamimetic[9] [sic, steroid] compounds listed in the claims on appeal." (*Id.*)

Appellants further argue that "[s]electing different parts of separate embodiments of the reference and combining them does not support anticipation," instead, "the reference must disclose a specific embodiment . . . one single embodiment, meeting all the claimed elements." (*Id.* at 18.) "Appellants further submit that one of ordinary skill in the art would not 'clearly envisage' from Germeyer's disclosure a specific embodiment which combines a specific compound of appellants' formula **1** with one of the recited betamimetics [sic, steroids]" (*id.* at 19), and argue that cases like *In re Petering* are distinguishable (*id.* at 19-20).

The issue with respect to this rejection is whether the description in Germeyer was sufficient to put the public in possession of the invention Appellants now claim.

Findings of Fact

We adopt the Examiner's findings concerning the scope and content of Germeyer's disclosure.

Principles of Law

The test which determines whether an invention has been anticipated by a reference is whether the description of the invention in the reference is "sufficient to put the public in possession of the invention." *In re LeGrice*, 301 F.2d 929, 933 (CCPA 1962); *In re Elsner*, 381 F.3d 1125, 1128 (Fed.

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[9] The Appeal Brief inadvertently substituted the term "biomimetics" where "steroids" was intended. (Reply 5.)

Cir. 2004) (applying *LeGrice*, and noting that "[i]n particular, one must be able to make the claimed invention without undue experimentation.").

A generic disclosure may anticipate a claim to a species within the generic disclosure. *E.g., In re Schaumann*, 572 F.2d 312 (CCPA 1978). The test for anticipation "is not an 'ipsissimis verbis' test." *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990).

Analysis

Germeyer's Example 6 explicitly described scopine 9-methylfluorene-9-carboxylate methobromide, and Germeyer claimed the compound in claim 23. It is undisputed that scopine 9-methylfluorene-9-carboxylate methobromide is a compound within Appellants' formula 1. Germeyer also claimed a pharmaceutical composition comprising scopine 9-methylfluorene-9-carboxylate methobromide in combination with corticosteroids, among other active substances. (Germeyer, claim 27.) We find no evidence that undue experimentation would have been required to follow Germeyer's instruction to make scopine 9-methylfluorene-9-carboxylate methobromide according to Example 6 and to follow Germeyer's further instruction to make a composition comprising it and any of the corticosteroids that Germeyer identified.

In view of the fact that Germeyer listed only 12 corticosteroids (Germeyer, col. 14), its disclosure to combine scopine 9-methylfluorene-9-carboxylate methobromide with anyone of those listed corticosteroids was effectively a disclosure of:

scopine 9-methylfluorene-9-carboxylate methobromide + flunisolide, scopine 9-methylfluorene-9-carboxylate methobromide + beclomethasone, scopine 9-methylfluorene-9-carboxylate methobromide + triamcinolone, and nine other specific combinations. Germeyer indicated that the steroid was "preferably" one of eight named, "while budesonide, fluticasone, momatasone and ciclesonide are important and budesonide and fluticasone are particularly important." (Germeyer, col. 14.) In short, of the 12 scopine 9-methylfluorene-9-carboxylate methobromide + steroid compositions that Germeyer effectively named, Appellants claim ten, plus another six. The ten of Appellants' compositions that Germeyer described would be "clearly envisaged" by a person of ordinary skill reading Germeyer. (Ans. 24.) We agree with the Examiner that the evidence supports a finding of anticipation for the compositions that Germeyer described.[10] That Appellants claim some but not all the compositions Germeyer described, and more, does not change our view. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985) ("when, as by a recitation of ranges *or otherwise*, a claim covers several compositions, the claim is 'anticipated' if one of them is in the prior art") (emphasis added).

We disagree with Appellants' argument that one of the opinions from *In re Arkley* (455 F.2d 586 (CCPA 1972)) should control the result here. In Appellants' view, *Arkley* made it a requirement that "[t]o support anticipation, the reference must disclose . . . one single embodiment, meeting all the claimed elements." (App. Br. 18.) In *Arkley*, four judges on

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[10] Appellants do not argue the claims separately, and we treat claim 1 as representative. Claims 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 therefore stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

a five member panel reversed an anticipation rejection, but the four did not join in a unanimous opinion. Two judges of the four member majority wrote an opinion setting out the idea Appellants favor. 455 F.2d at 807-10. However, the other two members of the majority wrote a concurring opinion in which they explicitly disagreed with their colleagues' legal theory and rejected the idea Appellants favor. 455 F.2d at 810-12 (Baldwin, J.). Thus, *Arkley* held that the anticipation rejection was reversed, but the court did not hold that to anticipate, a reference must literally disclose one single embodiment meeting all the claimed elements.

Six years after *Arkley*, the CCPA revisited the issue in the *Schaumann* case, and expressly repudiated the idea that *Arkley* set out the requirement that Appellants favor. *See Schaumann*, 572 F.2d at 317 ("*In re Arkley*, supra, should not be interpreted as establishing a new test for determining whether an invention has been described in a reference within the meaning of 35 U.S.C. § 102. See Judge Baldwin's concurring opinion." (Citation omitted)). Instead, the *Schaumann* opinion indicated that anticipation did not require an "ipsissimis verbis" test, 572 F.2d at 317, which continues to be the law, *see e.g. Bond*, 910 F.2d at 832.

Appellants argue that, given Germeyer, multiple selections must be made and combined from different parts of Germeyer's disclosure. (App. Br. 19.) We agree that selections must be made. However, the Examiner identified specific disclosures by Germeyer that taught exactly what combinations should be made. Among other disclosures, for example, Germeyer's claim 27 defines a composition comprising scopine 9-methylfluorene-9-carboxylate methobromide with an active substance selected from, among others, corticosteroids. Supporting the meaning of

that specific claim, Germeyer's specification lists 12 corticosteroids. Appellants now seek another patent on most of those corticosteroid combinations that Germeyer specifically taught. We disagree that a person of ordinary skill would be confused or baffled by Germeyer's plain disclosure of this subject matter. Instead, we think the Examiner's findings and response to Appellants' arguments are correct. *See Schaumann*, 572 F.2d at 316-17 (endorsing a similar analysis of prior art claim and specification).

NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

The Issue

The Examiner's position is that claims 1, 3, 5-8, 30 and 40 overlap in scope with, and are mutually obvious over, claims 1-7, 11-13, and 17 of copending Application No. 11/182,382 "in view of Germeyer '856." (Answer 15.) The rejection's explanation analyzes the appealed claims and the copending claims, but does not explain how the claims in Germeyer '856 are involved.

Appellants argue that Germeyer '856 "is not available as prior art for purposes of 35 U.S.C. § 103," which "means that the reference is also unavailable as a secondary reference to support an obviousness-type double patenting rejection." (App. Br. 21.) Appellants also argue that the provisional rejection should be withdrawn "at such time as the claims are otherwise found allowable." (*Id.* at 22.)

Analysis

Although the rejection is said to be "in view of" the Germeyer '856 patent, the Examiner explained the rejection exclusively in terms of the

appealed claims and the copending application claims, without explaining how Germeyer '856 is needed to support the rejection. In fact, neither the Examiner nor Appellants address the relevance of Germeyer '856 to the subject matter in the appealed claims. More importantly, Appellants do not dispute that the appealed and copending claims overlap, and do not dispute that the identified appealed and copending claims are mutually obvious.

We see no error in the Examiner's conclusions of overlap and mutual obviousness, and Appellants identify none. Accordingly, we find the analysis of overlap and mutual obviousness sufficient to affirm the rejection.

As the "primary" case for double patenting is undisputed, whether Germeyer '856 is "available" as a secondary reference is a superfluous question, and we find it unnecessary to reach it.

SUMMARY

We reverse the rejection of claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

We reverse the rejection of claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

We reverse the rejection of claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 112, second paragraph.

We affirm the rejection of claims 1, 3, 5-8, 26-30, 32, 35, 36, 39, 40 and 45-48 under 35 U.S.C. § 102(e) as anticipated by Germeyer '856.

We affirm the provisional rejection of claims 1, 3, 5-8, 30 and 40 on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 11-13 and 17 of copending Application No. 11/182,382.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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